Complete Summary

GUIDELINE TITLE

Newer drugs for epilepsy in children.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Newer drugs for epilepsy in children. London (UK): National Institute for Clinical Excellence (NICE); 2004 Apr. 39 p. (Technology appraisal; no. 79).

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse (NGC): This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

On April 19, 2005, Novartis Pharmaceuticals and the U.S. Food and Drug Administration (FDA) notified healthcare professionals about revisions to the WARNINGS and PRECAUTIONS sections of the prescribing information for TRILEPTAL (oxcarbazepine) tablets and oral suspension, indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ages 4-16 years with epilepsy. The updated WARNINGS section describes serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) that have been reported in both children and adults in association with Trileptal use. The PRECAUTIONS section has been updated to include language regarding multi-organ hypersensitivity reactions that have been reported in association with Trileptal use. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Epilepsy in children, including partial epilepsy with or without secondary generalisation, Lennox-Gastaut syndrome, infantile spasms, absence epilepsy, and benign (partial) epilepsy with centrotemporal spikes (BECTs)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Pediatrics

INTENDED USERS

Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assess the effectiveness and cost-effectiveness of newer drugs for children with epilepsy

TARGET POPULATION

Children with epilepsy

INTERVENTIONS AND PRACTICES CONSIDERED

1. Antiepileptic drug therapy as monotherapy or combination therapy:
    - Gabapentin
    - Lamotrigine
    - Oxcarbazepine
    - Tiagabine
    - Topiramate
    - Vigabatrin (as an adjunctive therapy for partial seizures)

2. Assessment of risks and benefits of drugs in girls of child-bearing potential
3. Referral to specialists in persons with first seizure
4. Review of and monitoring of treatment

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness (e.g., seizure frequency, seizure-free intervals)
- Adverse effects
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, The University of Birmingham (see the "Companion Documents" field).

Search Strategy

Studies employing the new antiepileptic drugs gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin were searched.

A scoping search was undertaken to identify existing and ongoing reviews.

Primary studies were identified using the following sources:

- Bibliographic databases. Since the National Health Service (NHS) Centre for Reviews and Dissemination (CRD) were undertaking a Technology Assessment Review (TAR) of newer drugs for epilepsy in adults, there was collaboration between the two centres, with the work shared as indicated and references exchanged.
    - MEDLINE (Ovid) 1966 - Oct 2001 (Bham)
    - MEDLINE and PreMEDLINE (Silverplatter) 1999 - March 2002 (NHSCRD)
    - EMBASE (Ovid) 1980 - Feb 2002 (Bham)
    - Cochrane Library (CCTR) 2002 Issue 1 (Bham)
    - Science Citation Index (Web of Science) 1981 - Feb 2002 (Bham)

    - National Research Register 2002 Issue 1 (Bham)
- Checking citations of relevant studies
- Contact with experts in the field
- Invited industry submissions

No date or language restrictions were placed on the literature searches.

Data for the economic model were identified by further searches of the following sources to identify existing decision analytic models, costs, cost effectiveness and quality of life:

- Bibliographic databases:
    - MEDLINE (Ovid) 1966 - Mar 2002
    - EMBASE (Ovid) 1980 - Mar 2002
    - NHS Economic Evaluation Database (EED)
    - NHS Database of Reviews of Effectiveness (DARE)
    - NHS CRD administration database (undertaken by NHSCRD)
    - Health Economic Evaluation Database (HEED) May 2002
- Internet sites of national health economic units.

Details of search strategies are provided in Appendix 7 page 158 of the assessment report.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Study design: Randomised controlled trials (RCTs) of any of the newer anti-epileptic drugs as mono-therapy or combined therapy for treatment of epilepsy.
- Study population: Persons with epilepsy under 18 years old and mixed age groups with epilepsy if including persons less than 18 years old.

Exclusion Criteria

- Trials recruiting only patients with single seizure, status epilepticus, seizures following surgery, febrile convulsions, trigeminal neuralgia or cortical myoclonus.

NUMBER OF SOURCE DOCUMENTS

Twenty trials were identified which reported outcome data for children with epilepsy; 15 have been published in full and 5 in abstract form only. Fifteen of the 20 trials identified used placebo as comparator, with 5 trials using active comparator treatments.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data Extraction Strategy

Two reviewers independently abstracted the data. A third reviewer resolved discrepancies. One reviewer screened foreign language publications using English abstracts if available. Translations were obtained where necessary. Studies with mixed age groups were identified during the inclusion/exclusion process. The data reported in these studies were categorised according to whether: 1) the study results report data for the different age groups separately; 2) the number of participants in different age-groups. Data for under 18s in these trials were extracted where possible.

Data was extracted on the following:

- Study design.
- Study population: (seizure types and frequencies, and epileptic syndrome); baseline comparability of intervention and control groups.
- Intervention and comparator including: drug; doses; mode of administration; duration of treatment.
- Outcomes measured including: identification of all outcomes which study protocols state would be measured; the specific measurement tool or data collection method; when, how and by whom the outcome data was collected; drop-outs; cross-overs and losses to follow-up for each outcome.
- Study results: as raw numbers where available, plus any summary measures with standard deviations, p-value and confidence intervals where reported.

Quality Assessment Strategy

The quality of RCTs was assessed by examining methods of randomisation, concealment of allocation, blinding, losses to follow up, and methods of analysis (intention to treat). Two reviewers independently examined trial quality.

Disagreements were resolved by consensus.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients, and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Cost Effectiveness

A commentary on company submissions that modelled childhood epilepsy and the Birmingham epilepsy model are provided in the assessment report.

The manufacturer submitted two economic analyses of lamotrigine in children. One was a simple decision tree with a 1-year time horizon comparing lamotrigine, carbamazepine and sodium valproate. See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- The newer antiepileptic drugs gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and vigabatrin (as an adjunctive therapy for partial seizures), within their licensed indications, are recommended for the management of epilepsy in children who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable because:
    - there are contraindications to the drugs
    - they could interact with other drugs the child is taking (notably oral contraceptives)
    - they are already known to be poorly tolerated by the child
    - the child is currently of childbearing potential or is likely to need treatment into her childbearing years (see below).

- Vigabatrin is recommended as a first-line therapy for the management of infantile spasms (West's syndrome).
- It is recommended that children should be treated with a single antiepileptic drug (monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. Caution is needed during the changeover period.
- It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with antiepileptic drugs (as above) have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the child, in terms of the balance between effectiveness in reducing seizure frequency and tolerability of side effects.
- In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the risk of the drugs causing harm to an unborn child, and the possibility of interaction with oral contraceptives, should be discussed with the child and/or their carer, and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data on which to base a definitive assessment of the risks to the unborn child associated with newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child.
- It is recommended that all children who have had a first non-febrile seizure should be seen as soon as possible by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs.
- Treatment should be reviewed at regular intervals to ensure that children with epilepsy are not maintained for long periods on treatment that is ineffective or poorly tolerated and that concordance with prescribed medication is maintained.
- The recommendations on choice of treatment and the importance of regular monitoring of effectiveness and tolerability are the same for specific groups, such as children with learning disabilities, as for the general population of children with epilepsy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Recommendations concerning clinical effectiveness are supported by 20 clinical trials, 15 of which have been published in full and 5 in abstract form only. Fifteen of the 20 trials identified used placebo as comparator, with 5 trials using active comparator treatments.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of newer drugs for children with epilepsy

POTENTIAL HARMS

Side effects of therapy, including the risk of the drugs causing harm to an unborn child and the possibility of interaction with oral contraceptives. For full details of side effects and contraindications, the reader is referred to the Summary of Product Characteristics for each antiepileptic drug.

CONTRAINDICATIONS

CONTRAINDICATIONS

For full details of contraindications, the reader is referred to the Summary of Product Characteristics for each antiepileptic drug.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

- All clinicians with responsibility for treating children with epilepsy should review their current practice and policies to take account of the guidance.
- Local guidelines, protocols or care pathways that refer to the care of children with epilepsy should incorporate the guidance.
- To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
    - A child with epilepsy is treated with a newer antiepileptic drug in the following circumstances.
        - He or she has not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate.
        - Older antiepileptic drugs are unsuitable because:
            - there are contraindications to the drugs
            - they could interact with other drugs the child is taking (notably oral contraceptives)
            - they are already known to be poorly tolerated by the individual
            - the child is of childbearing potential or is likely to need treatment into her childbearing years (see below).

        - Vigabatrin is considered as a first-line therapy for a child who has West's syndrome.
        - A child with epilepsy is ordinarily treated with a single antiepileptic drug. If the initial treatment of a child with epilepsy with a single antiepileptic drug (monotherapy) is unsuccessful, then he or she is treated with another single antiepileptic drug, with the changeover being carried out cautiously.
        - A child with epilepsy is prescribed combination therapy only when attempts at monotherapy with antiepileptic drugs have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, the child's treatment is reverted to the regimen that has proved most effective in reducing seizure frequency and has least side effects.
        - In girls of childbearing age, the risk of the drugs causing harm to an unborn child is discussed between the girl and/or her carer and the responsible clinician and an assessment is made as to the risks and benefits of treatment with individual drugs.
        - A child who has had a first non-febrile seizure is seen as early as possible by a specialist in the management of epilepsies.
        - Treatment is reviewed at regular intervals.
    - Local clinical audits could also include measurement of compliance with issues identified in the National Clinical Audit of Epilepsy-related Death and/or Improving Services for People with Epilepsy (the Department of Health response to the National Clinical Audit of Epilepsy-related Death), such as carrying out appropriate investigations to reach a diagnosis of epilepsy, supporting patients who are having problems with their drug regimens, and shared-care arrangements. Local audits may be able to make use of data already being collected for registries on epilepsy.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Newer drugs for epilepsy in children. London (UK): National Institute for Clinical Excellence (NICE); 2004 Apr. 39 p. (Technology appraisal; no. 79).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Apr

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Dr A E Ades, MRC Senior Scientist, MRC Health Services Research Collaboration, University of Bristol; Dr Tom Aslan, General Practitioner, Stockwell, London; Professor David Barnett (Chair) Professor of Clinical Pharmacology, University of Leicester; Professor Rosamund Bryar, Professor of Community & Primary Care Nursing, St Bartholomew School of Nursing and Midwifery; Dr Karl Claxton, Health Economist, University of York; Dr Richard Cookson, Senior Lecturer, Health Economics, School of Health Policy and Practice, University of East Anglia, Norwich; Professor Terry Feest, Clinical Director & Consultant Nephrologist, Richard Bright Renal Unit, & Chair of UK Renal Registry, Bristol; Professor Gary A Ford, Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust; Professor John Geddes, Professor of Epidemiological Psychiatry, University of Oxford; Ms Bethan George, Interface Liaison Pharmacist, Mile End Hospital, London; Mr John Goulston, Director of Finance, Barts and the London NHS Trust; Professor Philip Home, Professor of Diabetes Medicine, University of Newcastle upon Tyne; Dr Terry John, General Practitioner, The Firs, London; Mr Muntzer Mughal, Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust, Chorley; Judith Paget, Chief Executive, Caerphilly Local Health Board, Torfaen; Mr James Partridge, Chief Executive, Changing Faces, London; Mrs Kathryn Roberts, Nurse Practitioner, Hyde,

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Newer drugs for epilepsy in children. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Apr. 2 p. (Technology appraisal 79). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. Assessment report. West Midlands Health Technology Assessment Collaboration; 2003 Feb. 394 p. Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0549. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix C of the original guideline document.

PATIENT RESOURCES

The following is available:

- Newer drugs for epilepsy in children. Understanding NICE guidance - information for children with epilepsy, their families and carers, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2004 Apr. 12 p. (Technology appraisal 79).

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N0550. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on March 9, 2006.

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